REMARKS

Claims

Claims 13, 15 and 21–25 are currently under examination with claims 1–12, 16, and 20 withdrawn due to restriction/election and claims 14 and 17–19 cancelled without prejudice or disclaimer.

Claims 26–34 are added by this paper.

Claim amendments

Claim 13 has been amended. Sub-claims (a) and (b) have been amended according to conventional US practice. Support for sub-claims (c)-(e) can be found in the express disclosure contained in the Examples and the sequence listing page. See also, Applicants' analysis submitted herewith in Exhibits A-C. The minimal sequence identity, as recited in sub-claims (c)–(e) can be "at once envisaged" based on the teachings of the present application. See, for example, the explicit disclosure of the polypeptide clones (clones 1–11) and the sequences thereof (in reference to SEQ ID NO: 2) provided in the Examples section of the present application. See also, *In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962).

The functional element cancelled from claim 13 is now recited in claim 26.

The amendment of claim 21 is supported by the disclosure contained in page 16, lines 4–6 of the originally-filed specification.

Claim 22 has been recited in independent form.

The amendment of claim 23 and 25 is self-explanatory.

New claims 27–32 are drawn to the elected species, for example, pharmaceutical compositions and/or vaccines comprising the polypeptides of the present invention.

New claims 33–34 are supported at least, by the disclosure contained in the Examples. See, for example, pages 22–26 of the originally-filed specification.

It is respectfully submitted that the amendments do not raise new matter.

Claim objections

The Examiner is thanked for her careful review of the claims. The objection of claims 20 and 25 is moot in view of the amendments. Withdrawal of the objection is respectfully requested.

Rejections under §102(b)

The contention that claims 13, 15, 20–21 and 25 are anticipated by Fischer et al. (*Journal of Allergy and Clinical Immunology*, 1996) is respectfully traversed.

Fischer teaches decapeptide sequence of Phl p 4 containing ten amino acid residues (IVALPXGMLK) of the N-terminal region of Phl p 4. See, Fig. 5 and the description thereof at page 194 of Fischer et al. Fischer fails to teach or suggest the polypeptides of the present invention, for example, a polypeptides which comprise the sequences set forth in SEQ ID NO: 2, SEQ ID NO: 4, or SEQ ID NO: 6, or fragments thereof, as recited in present claim 13. Moreover, the cited reference fails to teach or suggest the structural elements of the polypeptides, comprising, for example, 50–350 amino acid residues. See, amended claim 21. Since not all elements of Applicants' claims are taught by Fischer, the cited reference fails to anticipate what is claimed herein. Withdrawal of the rejection is respectfully requested.

The contention that claims 13 and 23–24 are anticipated by Zhu et al. (US patent publication No. 2003/0135888) is respectfully traversed.

As acknowledged under item 14 at page 18 of the Office Action mailed December 3, 2007, Zhu teaches the polypeptide of SEQ ID NO: 298, which has *47.4% similarity* to SEQ ID NO: 2." Zhu's polypeptide does not meet the structural aspects of the claimed polypeptide molecules. See, amended claim 13. The rejection is therefore moot in view of the amendments. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, ¶2

The rejection, not specifically discussed herein, is moot in view of the amendments. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, ¶1

Reconsideration of the rejections made in the office action of December 3, 2007 is respectfully requested.

Applicant has reviewed the PTO's new *Written Description Guidelines* and maintains that the present claims are accordance with Example 10 beginning on Page 33 of the *Training Materials* (Rev. 1, March 25, 2008). See also, Example 6 at page 21 of the Guidelines. While applicants may not agree with the agency's interpretation of the elements necessary to meet the

statutory requirements of 35 U.S.C. § 112, ¶1, nonetheless, the pending claims have been amended to substantially conform to these.

The PTO's example provides a claim to a protein isolated from mouse liver that catalyzes the reaction A->B. The isolated protein was sequenced and its sequence was set forth in the specification as SEQ ID NO: 3.

Claim 1. An isolated protein comprising the amino acid sequence shown in SEQ ID NO: 3.

Claim 2. An isolated variant of a protein comprising the amino acid sequence shown in SEQ ID NO: 3, wherein the variant comprises an amino acid sequence that is at least 95% identical to SEQ ID NO: 3.

Claim 3. The isolated variant of claim 2, wherein the variant catalyzes the reaction A->B.

The guidelines state that claims 1 and 2 but not claim 3 satisfy the requirements set forth under §112, ¶1. However, with respect to claim 3, it should be noted that the exemplified specification "contemplated, but did not exemplify variants of the protein wherein the variant can have any or all of the following: *substitutions*, deletions, insertions and additions [in SEQ ID NO: 3]." In contrast to the exemplified specification, Applicants' specification discloses a vast number of polypeptide species which comprise the claimed activity. See, Table 6 at page 25 of the originally-filed specification and the disclosure in the Figures. To this end, the Examiner is courteously requested to review Example 11B at page 39 of the *Training Materials*. Although the subject matter discussed therein pertains to nucleic acid molecules, it is respectfully submitted that in view of the decision rendered on claim 2 of Example 11B, the entirety of Applicants' claims conforms with the PTO's published guidelines.

Thus it is respectfully submitted that the foregoing amendments render moot the written description rejection. The polypeptides are now claimed in terms of specific sequences. This is not to imply that the original claim scope was problematic under US law.

The contention that "Applicant has disclosed only the polypeptides of SEQ ID NO: 2, 4, [or] 6 encoded by SEQ ID NO: 1, 3 or 5" is incorrect. Applicants' specification provides a detailed disclosure of variant polypeptide molecules comprising one or more amino acid substitutions in the primary sequence of SEQ ID NO: 2. A total of eleven additional sequences (clones 1–11) are thus explicitly taught in these Examples. For example, clone 3 comprising P141, K282, L287, P299, L347, E351 variation in the polypeptide sequence of SEQ ID NO: 2, constitutes a variant polypeptide sequence whose structural information is expressly disclosed.

The structural information of other sequences can be similarly obtained. See, the paragraphs bridging page 24 and 25 of the present specification and the information provided in the sequence disclosure.

Sequence identity

A skilled artisan is thus in possession of the written description of both the nature (i.e., mutant or wild-type) as well as the structure (i.e., amino acid sequence) of the clone species disclosed in Table 6. Based on the information provided therein with respect to the polypeptide sequences, the skilled worker can ascertain the degree of sequence identity between the parent polypeptide of SEQ ID NO: 2 and the variant sequences (i.e., sequences comprising the recited amino acid variations in clones 1-11). Such techniques, comprising for example, computer assisted (i.e., BEST FIT) analysis or experimental analysis (i.e., hybridization under stringent conditions to a given polynucleotide and/or immunological cross-reactivity of the encoded polypeptide) were known in the art as of the filing date of the present application. Applicants' own specification provides a disclosure of such techniques. See, page 11, ¶3. Therefore it is respectfully submitted that the recited percent identity to a given sequence, for example, SEQ ID NO: 2, can thus be "at once envisaged." Explicit disclosure is not necessary. See, *Capon v. Eshhar v. Dudas*, (Fed. Cir. 2005) 418 F.3d 1349, 76 U.S.P.Q.2d 1078 (discussed *infra*).

Submitted herewith are exhibits disclosing the calculated sequence identities between the polypeptide molecules of the instant invention (in matrix form). In Exhibit A, full-length polypeptide sequences (for example, SEQ ID NO: 2, 4, 6 and the polypeptide sequences of the 11 different clones) have been compared. In Exhibits B and C, specific polypeptide fragments (of 144 amino acid residues and 33 amino acid residues, respectively) have been compared. It can be ascertained, for example, that the polypeptide of clone 3 comprising P141, K282, L287, P299, L347, E351 variation in the polypeptide sequence of SEQ ID NO: 2 has 98.8% sequence identity with that of SEQ ID NO: 2. The minimal structural identity between the claimed species of polypeptide molecules, for example, clone 1 and clone 9 (items 4 and 12 in the chart) is thus readily determined to be 90.8%. The structural features claimed herein, for example, sequence identity to a given polypeptide species, need not be explicitly disclosed in the instant application insofar as a generic teaching of such homologs and methods of determining the common structural features (i.e., sequence identity) have been provided. See, e.g., *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies,*

Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). See, also, MPEP §2164.05(a).

Therefore claimed polypeptide molecules having the recited minimal sequence identity with the polypeptides of SEQ ID NO: 2 [see, sub-claim (c) of claim 13] or specific portion thereof [see, sub-claims (d) and (e) of claim 13] was taught by Applicants' own specification.

Enablement

Applicant respectfully traverses the PTO's contention that "the skilled artisan would not reasonably expect *anything less than 100% identity* over the full length of SEQ ID NO: 2, 4 or 6 to share the same function as the polypeptide of SEQ ID NO: 2, 4 or 6." In view of the aforementioned arguments and remarks, this contention is baseless.

Applicants' claims are directed to polypeptide molecules and fragments thereof comprising specific sequences. Variants of the claimed molecules, comprising, for example, the claimed sequence identity to a given polypeptide of SEQ ID NO:2, are further disclosed. The detailed disclosure contained in Applicants' specification (as substantiated by the disclosure of three polypeptide sequences and 11 other clonal variants) provides a detailed description of the structure/activity of the claimed variant sequences. Structures (for example, amino acid sequences) of the claimed group 4 *Poaceae* allergens and clones thereof are provided in the sequence listing page and the table at page 25. The biological activities of such polypeptide molecules, for example, with respect to their reactivity to IgE molecules, are also disclosed. See, the disclosure in Fig. 5 and the description thereof at page 6 of the present application.

Variant polypeptide sequences

Applicants invite the Examiner to review a recent precedential opinion issued by the United States Board of Patent Appeals and Interferences (*Ex parte* Kubin, B.A.P.I. 2007), a copy of which is enclosed herewith.

The facts in Kubin are applicable to the present case. In Kubin, the Examiner contended that "at least 80% identity language" in the absence of any working examples, other than a few representative species, fails to provide enablement of the claimed genus of molecules. See, page 10 of *Ex parte* Kubin. The Examiner alleged that specification did not teach "which 20% . . . of amino acid residues should be changed in order to maintain the biological functions." In response, Appellants argued that the specification disclosed "in detail how to: 1) make variants of

SEQ ID NOs: 1 and 2; 2) calculate the percent identity between SEQ ID NOs: 1 and 2 and the variant sequence; and 3) test the variant sequence to determine [functional activity]." See, items 23 and 24 at page 13. Appellants further argued that in view of the high level of skill in molecular biology, methods of making the claimed nucleic acid sequences and screening for activity [were] known in the art and described in the specification and that the "experimentation involved to produce other sequences within the scope of the claims" and thus to practice the full scope of the claims would have been "well within the skill of those in the art." The amount of experimentation involved would have been routine and not undue. See, items 27–30 at page 14.

The Board of Patent Appeals and Interferences in reversing the enablement rejection concluded:

> "The amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those skilled in the art. *See, e.g., Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1360, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998) ("test [for undue experimentation] is not merely quantitative . . . if it is merely routine"). A "patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). Thus, we conclude the Specification would have enabled the full scope of claim 73. (Emphasis added)

Likewise in the present application, Applicants disclose a genus of Phl p 4 (group 4 allergens) polypeptides having a disclosed primary structure and polynucleotides encoding such polypeptides. Methods of obtaining other polynucleotide sequences, for example, polynucleotides which hybridize to Phl p 4 polynucleotides of SEQ ID NO: 1, 3 and 5 under stringent hybridization conditions, were known in the art. Techniques for isolating polypeptide variants encoded by such hybridizing polynucleotides and methods for testing of such variant species based on claimed activity were all known in the art.

For example, a skilled artisan could routinely utilize translation techniques for identifying polypeptides which are encoded by such hybridizing polynucleotides (for example, using translation tools) and whether such polypeptides would meet the structural aspect(s) recited in Applicants' claims. The exhibits enclosed herewith provide an example via which variant sequences of Table 6 and/or fragments thereof may be analyzed with respect to the sequence identity to a given polypeptide sequence of SEQ ID NO: 2. Polypeptide sequences which meet the recited structural aspect(s) (for example, at least 90.8% sequence identity) could then be expressed and assayed for claimed IgE activity using art-known techniques, for example,

immunoblotting techniques. See, for example, the disclosure contained in Fig. 5. It would be routine that such polypeptides could be isolated and used by one of ordinary skill in the art using the methods recited in the instant application. Therefore, the level of "experimentation involved to produce other sequences within the scope of the claims" and thus to practice the full scope of the claims would have been "well within the skill of those in the art."

With respect to testing of the variant sequences, reference is made to several art publications which exemplify the various methods and high level of skill in the art that existed at the time the present application was filed for identifying such molecules. These references provide ample evidence that routine protocols for epitope mapping were available and being employed in a variety of fields prior to and at the time of the filing of the present application. For example, Livingstone et al. (*Ann. Rev. Immunol.*, vol. 5, 477-501, 1987) describe routine methods for identifying T cell epitope and provide models for predicting T cell epitopes in a protein on the basis of the primary sequence alone.

Moreover, synthesis of large arrays of unique peptides and use of such libraries for screening variants was routine in the art. For example, Geysen (*PNAS*, 81, 3998-4002. 1984) describes a method, subsequently referred to as "the pin method" or "the Pepscan method", which allows for the rapid, concurrent synthesis on polyethylene rods of hundreds of peptides of sufficient purify for ELISA assays. The screened peptides were mapped to eptitopes of foot-and mouth disease virus coat protein involved in antibody binding. Subsequent publications by the same author expressly account for the routineness of the procedure. "The current methodology requires only basic skills in organic chemistry, and can be used to synthesize more than 2000 peptides (hexapeptides) per 10 working day." Geysen et al. further state their group "presently tests about 4000 peptides each working day." See, Geysen et al., *J. Immunol. Methods*, 259-274, 1987. Van der Zee et al. (*Eur. J. Immunol.* 1989. 19:43-47) modified the Pepscan method so that the synthetic peptides could be released from the solid phase support, for direct use in T cell stimulation assays. Van der Zee used this modified technique to finely map a T-cell epitope in the mycobacterial 65 kDa heat shock protein. Likewise, Maeji et al. used the Pepscan methodology to map T cell epitopes of tetanus toxin (Maeji, et al., Multi-pin peptide synthesis strategy for T cell determinant analysis. *J. of Immunol. Methods*, 134, 23-33. 1990). Since 1993, the Pepscan technique has been made commercially available in kit form by Cambridge Research Biochemicals, Cambridge, UK. For example, Cason used the Pepscan kit to map

immunodominant epitopes of the bovine papillomavirus major (L1) capsid protein. (Cason et al., *J. Gen. Virol.*, 74, 2669-2677, 1993). Likewise, Ebner et al. utilized the Pepscan method to identify multiple T cell epitopes on the major birch pollen allergen Bet vl. (*J. of Immunol.*, 150, No.3, 1047-1054. 1993).

In addition to the Pepscsan method, Houghten taught a method for synthesizing large numbers of peptides on standard, amino acid resin that was sealed in packets (the "teabag" method). See, Houghten et al., *PNAS*, 82, 5131-5135, 1985. Using this method, the synthetic peptides could be easily cleaved from the resin allowing them to be used in liquid phase assays. Houghten used this method to simultaneously synthesize 248 different peptides from the influenza hemagglutinin protein (HA1), which were then used to map amino acids involved in the binding of anti-HA1 antibody. Houghten further states that his technique is simple and can be used to perform greater than 1000 syntheses simultaneously. Oftung et al. utilized the method of Houghten to map human T cell epitopes on the Mycobacterium tuberculosis 65-KD protein antigen (*J Immunol.*, 141, 2749-54, 1988). As an alternative to protein synthesis, the generation of peptides from a known protein sequence could have been achieved by genetic manipulation of nucleic acid molecules encoding the protein of interest. Relevant techniques include, for example, the use of frequently and non-frequently cutting, restriction enzymes to generate fragments of a nucleic acid molecule encoding the protein of interest; the use of timed exonuclease III and/or Dnase I digestions of a nucleic acid molecule encoding the protein of interest; and the use of the polymerase chain reaction to generate precise fragments of the open reading frame encoding the protein of interest. All of these techniques were being employed at the time of filing. The methodology for performing the aforementioned techniques is further provided in rich detail in Methods in Molecular Biology, vol. 66, Epitope Mapping Protocols, 1996.

Not only was it possible to easily generate a multitude of peptides from a known protein, but techniques for high-volume screening of such fragments and peptides for T cell epitopes were clearly available. For instance, such screening could have been achieved by measuring T-cell proliferation in response to peptides in combination with antigen presenting cells. Many of the references already mentioned describe such assays. For example, the aforementioned Van der Zee, Ebner, Ofung, and Lamb references, all teach assays using 3H-thymidine uptake by T cells as a way of measuring cell proliferation. Methods for assaying large number of samples, for example, employing a 96-well micro-plate, are also provided. It should be noted that plates

having a higher density of wells (e.g., 384 wells) along with the use of automated readers capable of handling such platforms were available to the skilled worker as of the filing date of the instant application. In addition, several methodologies were being used to increase the efficiency of such screening and/or isolation of peptides of interest.

Accordingly, it is respectfully submitted that at the time the present application was filed, routine methods were available to screen for specific epitopes and to test the effects contributed by the addition of each amino acid residue to a given epitope. For example, Focke et al. 2001 (cited in the Office Action) disclose Phi p 1 IgE eptitopes and the functional background of generating peptides with reduced IgE reactivity (for example the destruction or deletion of IgE epitopes). Also Schramm et al. 1999 (see specification on page 3, first paragraph) disclose mutated recombinant allergens in which IgE eptiopes are specifically deleted without impairing the T cell eptitopes, which are essential for therapy.

Claims directed to the pharmaceutical composition/vaccines

In the paragraphs bridging pages 11 and 12, the Office Action alleges that the pharmaceutical compositions and/or vaccines of the present invention are non-enabled. This contention is respectfully traversed.

At the outset, Applicants courteously submit that the Office Action fails to present any evidence which suggests the pharmaceutical compositions, as claimed herein, are not enabled. In the absence of such evidence, the rejection is deficient under controlling case law.

The burden is upon the Patent and Trademark Office to provide evidence shedding doubt that the invention can not be made and used as stated; see for example, In re Marzocchi, 439, F. 2d 220, 169 USPQ 367 (CCPA 1971). Moreover, Applicants' specification teaches that molecules of the present invention are useful formulation of vaccines and/or pharmaceutical compositions. See the generic teachings offered in the paragraph bridging page 15 and 16 of the present application.

In relation to a disclosure on the utilization of Phl p 4 polypeptides as a pharmaceutical composition, the Examiner is courteously invited to review the disclosure contained in the Examples of the present application. See, for example, the paragraphs bridging page 7, line 28 to page 8, line 24 of the instant specification, as originally filed. In this regard, Applicants' specification expressly teaches that fragment and/or recombinant forms of allergens, which exhibit a different IgE reactivity profile compared to the natural allergen (nPhl p 4), can be

utilized as pharmaceutical compositions or vaccines. Rationale for the use of the molecules of the instant invention in the desensitization of a subject suffering from allergy is also provided. See, the page 15, lines 9–27; page 16, lines 19–24 of the specification, as originally filed.

Moreover, the disclosure in page 8, lines 3–17 of Applicants' specification and the cited Schramm reference expressly teach that the use of hypoallergenic peptide molecules, such as the rPhl p 4 variant polypeptide of the present invention, for therapy of allergic diseases was appreciated by one of ordinary skilled in the art. To this end, the Examiner is also cordially requested to review the entirety of disclosure contained in the cited reference of Fischer et al. (*Journal of Allergy and Clinical Immunology*, 1996).

Thus it is respectfully submitted that the specification provides an enabling disclosure on the claimed allergenic properties of the Phl p 4 polypeptides of the instant invention. Therefore, the specification's express teaching that the claimed compounds are pharmaceutically useful is clearly credible as required. The PTO's contentions regarding non-enablement based on the "unpredictability" and "lack of working examples" are especially weak in view of the detailed disclosure contained in Applicants' own specification and the state of the art before the earliest filing date of the instant application. Withdrawal of the rejection is respectfully requested.

Based on the aforementioned remarks and arguments, further in view of the amendments presented herein, it is respectfully submitted that Applicants' specification provides an enabling disclosure of what is claimed by the present invention. Withdrawal of the rejection under 35 U.S.C. §112, ¶1, is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

No fees are believed to be due with this response; however, the Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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